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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,574	11/14/2003	Jeffrey M. Isner	47624-DVC (71417)	1777

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,574	ISNER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 49-66 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 49-66 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 7/16/04 is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/3/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' preliminary amendment filed on 7/16/04 has been entered.

New claims 49-66 are pending in the present application, and they are examined on the merits herein.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 49 and its dependent claims recite the limitations "A method for inducing new blood vessel growth in myocardial tissue of a mammal in need thereof such treatment"; "inducing the new blood vessel growth in the myocardial tissue of the mammal" and "colony stimulating factor (CSF)". In addition, claim 61 further recites the following limitation "the method further comprises administering to the mammal an anti-coagulant before, during, or after administration of the nucleic acid to the mammal".

There is literally **no written support** for a method with the aforementioned limitations as claimed in the originally filed specification of the US patent application with

Serial No. 09/265,041, filed on 3/9/1999, now issued US Patent 6,676,937, which the instant application is a division of. The originally filed specification discloses a method for treating **myocardial ischemia** or **ischemic cardiomypopathy** (page 15, lines 1-10; also pointed out by Applicants' remarks), and **not any other myocardial tissue such as a non-ischemic myocardial tissue or a myocardial tissue suitable for transplantation**. While the originally filed specification teaches embodiments in which co-administration of a DNA encoding an angiogenic or hematopoietic protein is desired **with GM-CSF or with other vascularization modulating agents such as Steel factor, G-CSF, M-CSF, HGF, b-FGF** (page 19, lines 10-32; page 20, lines 5-11; page 21, lines 13-25), it does not support a concept for a co-administration of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof **with a colony stimulating factor (CSF) or an effective fragment thereof**. Please note that a colony stimulating factor is not necessarily limited to G-CSF or M-CSF because it may encompass other proteins and peptides which can act on macrophages and are capable of modulate vascularization. The originally filed specification identifies a colony stimulating factor as an endothelial cell mitogen (page 23, line 28 continues to line 1 of page 24) and as an angiogenic protein (page 20, lines 12-26), and **not as a vascularization modulating agent.** The passages cited by Applicants (e.g., page 21, last line to page 23, line 5; page 23, line 25 to page 24, first line) also do not support such a concept. The examiner also could not find any written support for the method step of further administering to the mammal **an anti-coagulant before, during, or after administration of a nucleic acid encoding at least one angiogenic protein or an**

effective fragment thereof. Nor do Applicants point out where in the originally filed specification one can find a written support for such a concept.

Therefore, given the lack of guidance provided by the originally filed specification, it would appear that Applicants did not contemplate or have possession of the claimed invention at the time the application was filed.

Should Applicants overcome the above New Matter Rejection, the instant claims are only entitled **at best to the effective filing date of 3/9/1999** because the provisional application 60/077,262, filed on 3/9/1998 does not have a written support for the administration of a stem cell factor (SCF) into any mammal or a concept for a co-administering any colony stimulating factor (CSF) other than a GM-CSF with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50-51 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 50 and its dependent claims, the phrase "the angiogenic factor" renders the claims indefinite. This is because which angiogenic factor do Applicants refer to? In

claim 49 from which claim 50 is dependent, "angiogenic protein" and not "angiogenic factor" is recited. Clarification is requested because the metes and bounds of the claims are not clearly determined. For the purpose of a compact prosecution, the examiner assumes that Applicants refer to the angiogenic protein in claim 49.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 49-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307) in view of Hammond et al. (US Patent 5,880,090; IDS).

Isner teaches a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia,

pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and myocardial ischemia (page 4, lines 5-23). The method comprises the step of injecting said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein by any injection means, and the nucleic acid may be carried by vehicles such as cationic liposomes, adenoviral vectors and that nucleic acid encoding different angiogenic proteins may be used separately or simultaneously (page 4, line 25 continues to line 8 of page 5). Angiogenic protein includes aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxidesynthase or muteins or portions thereof (page 5, lines 10-22). Isner also teaches that the nucleic acid encoding an angiogenic protein is inserted into a cassette where it is operably linked to a promoter that is capable of driving expression of the protein in cells of the desired target tissue (page 9, line 28 continues to line 20 of page 10). Isner further teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing angiogenesis, including, for example, nitric oxide synthase, L-arginine, fibronectin, urokinase, plasminogen activator and heparin (page 11, lines 15-19). Isner also discloses that catheters have been used for gene delivered in the art (page 1, line 23 continues to line 30 of page 2).

Isner do not specifically teach the administration of an effective amount of a stem cell factor (SCF), a colony stimulating factor (CSF) or an effective fragment thereof into the mammal with an effective amount of a solution comprising a nucleic acid encoding

at least one angiogenic protein or an effective fragment thereof, even though Isner teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells.

At the effective filing date of the present application Hammond et al already teach that cytokines such as stem cell factor (SCF), granulocyte-macrophage conlony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient (see at least Summary of the invention). Hammond et al further note that CD34+ circulating cells in the blood can participate in the repair of ischemic tissue (col. 3, lines 28-37).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Isner by further administering to the treated mammal an effective amount of at least one of SCF or CSF or an effective fragment thereof in light of the teachings of Hammond et al, and since Isner also teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, including nitric oxide synthase which is an angiogenic protein or factor (page 11, lines 15-19; and page 7, lines 16-24).

An ordinary skilled artisan would have been motivated to carry out the above modification because Hammond et al. already demonstrated that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for

increasing endothelialization in a treated patient; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the therapeutic outcome. The modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner and Hammond et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 49-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307) in view of Bussolino et al. (J. Clin. Invest. 87:986-995, 1991; IDS).

The teachings of Isner have been presented above. However, Isner do not specifically teach the administration of an effective amount of a colony stimulating factor (CSF) or an effective fragment thereof into the mammal with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof, even though Isner teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells.

At the effective filing date of the present application Bussolino et al already demonstrated that human recombinant G-CSF and GM-CSF are capable of inducing

endothelial cells to proliferate and migrate *in vitro*, with recombinant G-CSF has angiogenic activity *in vivo*. Additionally, recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis (see abstract and Methods).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Isner by utilizing recombinant G-CSF as an endothelial cell mitogen to be administered to a patient in need thereof in light of the teachings of Bussolino et al, and since Isner also teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, including nitric oxide synthase which is an angiogenic protein or factor (page 11, lines 15-19; and page 7, lines 16-24).

An ordinary skilled artisan would have been motivated to carry out the above modification because Bussolino et al. already demonstrated that recombinant G-CSF has angiogenic activity *in vivo*, and that it also exhibits synergistic effects with at least another endothelial cell mitogen bFGF in inducing *in vivo* angiogenesis. This would in effect optimize the desired therapeutic outcome. The synergistic effects in the induction of angiogenesis would also be reasonably expected for the interaction between the administered G-CSF and encoded bFGF or its fragment being expressed from a delivered nucleic acid. The modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner and Bussolino et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 49-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49, 52-56, 58-65 and 68 of copending Application No. 10/696,391.

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are directed to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment comprising: a) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one of: stem cell factor (SCF), colony stimulating factor (CSF) or an effective fragment thereof, thereby inducing

the new blood vessel growth in the myocardial tissue of the mammal; whereas claims 49, 52-56, 58-65 and 68 of copending Application No. 10/696,391 are drawn to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment comprising: a) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal.

The claims of the present application differ from the claims of the copending Application No. 10/696,391 in reciting administering to the mammal an effective amount of at least one of: stem cell factor (SCF), colony stimulating factor (CSF) or an effective fragment thereof. The claims of the present application can not be considered to be patentably distinct over claims 49, 52-56, 58-65 and 68 of copending Application No. 10/696,391 when there is a specific disclosed embodiment of the co-pending application that teaches that SCF and CSF or their fragments are angiogenic proteins or factors contemplated by Applicants; and claim 58 of the co-pending application specifically recites SCF and CSF or their fragments as desired angiogenic factors. Accordingly, the claims of the copending Application No. 10/696,391 fall within the scope of claims 49-66 of the present application.

This is because it would have been obvious to an ordinary skilled artisan to modify the method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment in the co-pending application by utilizing SCF and/or

CSF or fragments thereof as angiogenic factors that support the instant claims. An ordinary skilled artisan would have been motivated to do this because these embodiments are explicitly disclosed in the co-pending application are preferred embodiments.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D
PATENT EXAMINER